## *Remarks*

Reconsideration of this Application is respectfully requested.

Applicant respectfully requests that this Reply under 37 C.F.R. § 1.111 be entered by the Examiner. Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Election of Species Requirement***

Provisional election of species was made on December 2, 2005 (not November 25, 2005 as referred to in the Office Action) during a telephone conversation with the Examiner. Applicant provisionally elected to prosecute the following elected species: 4-(4'-fluorophenoxy)benzaldehyde semicarbazone as the first agent in the claimed method of treatment, and gabapentin as the second agent in the claimed method of treatment. Applicant hereby affirms this election of species. Claims 10-21, 34-45, and 50-52 read upon this elected species.

The Examiner has withdrawn claims 22-33 and 46-49 from further consideration as being drawn to a non-elected invention. Applicant asserts the right to claim additional species in the event that a generic claim hereto is found allowable in accordance with 37 C.F.R. § 1.141(a).

***Rejection Under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 10-21, 34-45, and 50-52 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wang *et al.* (Published International Appl.

No. WO 98/47869) ("Wang") in view of Bryans *et al.* (*Medicinal Research Reviews 19(2)*:149-177 (1999)) ("Bryans"), and further in view of Applicant's allegedly admitted prior art (page 3, line 10 through page 4, line 5 of the specification) and Singh (U.S. Patent No. 6,001,876). Applicant respectfully traverses this rejection.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious, but whether the claimed invention as a whole would have been obvious. *See* M.P.E.P. § 2141.02.

The Examiner suggests that Wang differs from the claimed invention because Wang fails to disclose the use of gabapentin in combination with a sodium channel blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (a/k/a Co 102862) in treating chronic pain. The Examiner alleges that "[t]o incorporate such a teaching into the teaching of Wang, would have been obvious in view of Bryans who teaches the use of gabapentin for treating chronic pain."

The Examiner concludes:

> The . . . references in combination make clear that the sodium channel blocker (i.e., 4-(4'-fluorophenoxy)benzaldehyde semicarbazone) and gabapentin have been individually used for the treatment of chronic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the

additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)* (Office Action at page 5, lines 10-16).

Applicant respectfully disagrees. In *Kerkhoven*, the claimed invention was rejected because the Examiner "concluded that the mere mixing of two compositions each taught for the same purpose, *in the absence of a showing of unexpected results*, is obvious." *In re Kerkhoven*, 205 U.S.P.Q. at 1071 (emphasis added). In contrast to Kerkhoven's invention, the present invention demonstrates a synergistic effect between the two co-administered components, *i.e.*, an effect greater than what would have been expected from merely adding the effects of the two components administered individually. *See* Applicant's specification, Example 1, page 32, line 24 through 33, line 2, and Figure 1. Figure 1 shows that the withdrawal thresholds at the time 2 hours after administration of (i) the sodium channel blocker, 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (i.e., Co 102862), (ii) gabapentin, and (iii) the combination of the two compounds are 10^0.30=2.00 gms, 10^0.62=4.17 gms and 10^0.96=9.12 gms, respectively. These calculations show the taking of the antilogarithm of Figure 1 ordinate values, which are reported as their $base_{10}$ logarithms.

If there was only an additive effect, the expected withdrawal threshold for the combination treatment would be 2.00 gms + 4.17 gms = 6.17 gms. This would be significantly smaller than the actual reported value for the combination treatment of 9.12 gms and, thus, the combination treatment appears to show a synergistic effect.

Accordingly, the data presented in Applicant's specification demonstrates that the tactile anti-allodynia effect of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) *p.o.* and gabapentin *s.c.* administered in combination is not merely additive of

the two individual components, but rather is greater than the sum of the individual compound's effects. In view of this experimental result, Applicant respectfully submits that none of claims 10-21, 34-45, or 50-52 is rendered obvious by the teachings of Wang and Bryans, either alone or in combination.

Applicant's description in the specification, on page 3, line 10 through page 4, line 5, merely serves to describe, *inter alia*, a recent demonstration of gabapentin as useful in treating chronic pain (Rowbotham *et al.* (1998); Backonja *et al.* (1998)). Singh purportedly describes the effect of gabapentin on chronic pain. Applicant respectfully submits that neither the references cited in the instant specification nor Singh remedies the deficiencies of Wang and Bryans.

Subsequent to the filing of the instant application, other groups working in the field have also demonstrated a synergistic effect for combinations of gabapentin with other sodium channel blockers. Applicant submits herewith a Supplemental Information Disclosure Statement citing document AM5, International Application Publication No. WO 03/020273 (hereafter "the '273 publication"). According to the '273 publication, compositions comprising a sodium channel blocker α-aminoamide and gabapentin, pregabalin or tiagabine have improved properties for the therapy of pain. The Examiner's attention is respectfully directed to the fact that, while not every combination tested according to the '273 publication showed synergy, the '273 publication demonstrates that gabapentin administered with another sodium channel blocker, *i.e.*, (S)-(+)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide (NW-1029), (R)-(-)-2-[4-benzyloxybenzylamino]-3-phenyl-N-methylpropanamide (NW-1037), or (S)-(+)-2-[4-(3-

fluorobenzyloxy)-benzylamino]-N-methyl-propanamide (NW-1043), is likely to provide a synergistic effect when administered for chronic pain.

In view of all of the above remarks, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 10-21, 34-45, and 50-52.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

In view of the foregoing remarks, Applicant submits that the claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicant therefore requests the entry of this Reply, as well as the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Applicant believes that a full and complete reply has been made to the outstanding Office Action and that, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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